Medications for Chronic Asthma

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Chronic asthma is a major health concern for children and adults worldwide. The goal of treatment is to prevent symptoms by reducing airway inflammation and hyperreactivity. Step-up therapy for symptom control involves initiation with low-dose treatment and increasing intensity at subsequent visits if control is not achieved. Step-down therapy starts with a high-dose regimen, reducing intensity as control is achieved. Multiple randomized controlled trials have shown that inhaled corticosteroids are the most effective monotherapy. Other agents may be added to inhaled corticosteroids if optimal symptom control is not initially attained. Long-acting beta$_2$ agonists are the most effective addition, but they are not recommended as monotherapy because of questions regarding their safety. Leukotriene receptor antagonists can be used in addition to inhaled corticosteroids, but they are not as effective as adding a long-acting beta$_2$ agonist. Patients with mild persistent asthma who prefer not to use inhaled corticosteroids may use leukotriene receptor antagonists as monotherapy, but they are less effective. Because of their high cost and a risk of anaphylaxis, monoclonal antibodies should be reserved for patients with severe symptoms not controlled by other agents. Immunotherapy should be considered in persons with asthma triggered by confirmed allergies if they are experiencing adverse effects with medication or have other comorbid allergic conditions. Many patients with asthma use complementary and alternative agents, most of which lack data regarding their safety or effectiveness. (*Am Fam Physician*. 2016;94(6):454-462. Copyright © 2016 American Academy of Family Physicians.)

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▶ **Patient information**: A handout on this topic is available at http://familydoctor.org/familydoctor/en/diseases-conditions/asthma/treatment.html.

Approximately 25.7 million persons in the United States, including 7 million children, had the diagnosis of asthma as of 2010.[1] It is reported that 4.1 million children experienced at least one asthma exacerbation in 2011.[2] Between 1995 and 2010, exacerbations accounted for one-third of all hospital admissions for children younger than 15 years.[3] Asthma caused 3,345 U.S. deaths in 2011,[4] and it accounts for $50.1 billion annually in direct health care costs.[5] The management of asthma involves care plans, chronic medications, and monitoring and self-care for acute exacerbations. Therapeutic agents used in the chronic management of asthma aim to prevent symptoms by controlling airway inflammation and hyperreactivity. This article reviews the currently available medications and complementary agents for chronic asthma management. A previous article in *American Family Physician* discussed the management of acute exacerbations.[6]

Assessment

To provide appropriate long-term medication, physicians should assess asthma severity and symptom control at diagnosis and at each subsequent visit using one of several validated tools, such as the Asthma Control Test (https://www.asthma.com/additional-resources/asthma-control-test.html).[7-9] The 2007 National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program Expert Panel Report 3 (EPR-3) recommends classifying disease severity based on level of impairment and risk of adverse events *(Figure 1, eFigure A, and eFigure B)*.[10] Once disease severity is determined, the physician must then decide on medication and self-care management options.

Step-Up and Step-Down Therapy

Two general approaches when choosing asthma medication regimens are step-up and step-down therapy *(Figure 2, eFigure C, and eFigure D)*.[10] Step-up therapy involves initiating treatment at a low dose and assessing

Classifying Asthma Severity in Children 12 Years and Older and Adults

Classifying severity for patients who are not currently receiving long-term control medication*

Components of severity		*Classification of asthma severity*			
		Intermittent	*Persistent*		
			Mild	*Moderate*	*Severe*
Impairment Normal FEV_1/FVC: 8 to 19 years = 85% 20 to 39 years = 80% 40 to 59 years = 75% 60 to 80 years = 70%	Symptoms	≤ 2 days per week	> 2 days per week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤ 2 times per month	3 to 4 times per month	> 1 time per week but not nightly	Every night
	Short-acting $beta_2$ agonist use for symptom control (not prevention of EIB)	≤ 2 days per week	> 2 days per week but not > 1 time per day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	Normal FEV_1 between exacerbations FEV_1 > 80% predicted FEV_1/FVC normal	FEV_1 ≥ 80% predicted FEV_1/FVC normal	FEV_1 > 60 % but < 80% predicted FEV_1/FVC reduced 5%	FEV_1 < 60% predicted FEV_1/FVC reduced > 5%
Risk	Exacerbations requiring oral systemic corticosteroids	0 to 1 per year†	≥ 2 per year†	≥ 2 per year†	≥ 2 per year†
		Consider severity and interval since last exacerbation; frequency and severity may fluctuate over time for patients in any severity category			
		Relative annual risk of exacerbations may be related to FEV_1			

Classifying severity in patients after asthma becomes well controlled, by lowest level of treatment required to maintain control‡

	Classification of asthma severity			
	Intermittent	*Persistent*		
		Mild	*Moderate*	*Severe*
Lowest level of treatment required to maintain control (see Figure 2 for treatment steps)	Step 1	Step 2	Step 3 or 4	Step 5 or 6

**—Level of severity is determined by assessment of impairment and risk. Assess impairment domain by patient's or caregiver's recall of previous two to four weeks and spirometry. Assign severity to the most severe category in which any feature occurs.*

†—At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or admission to intensive care unit) indicate greater underlying disease severity. For treatment purposes, patients who had at least two exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

‡—For population-based evaluations, clinical research, or characterization of a patient's overall asthma severity after control is achieved. For clinical management, the focus is on monitoring the level of control, not the level of severity, once treatment is established.

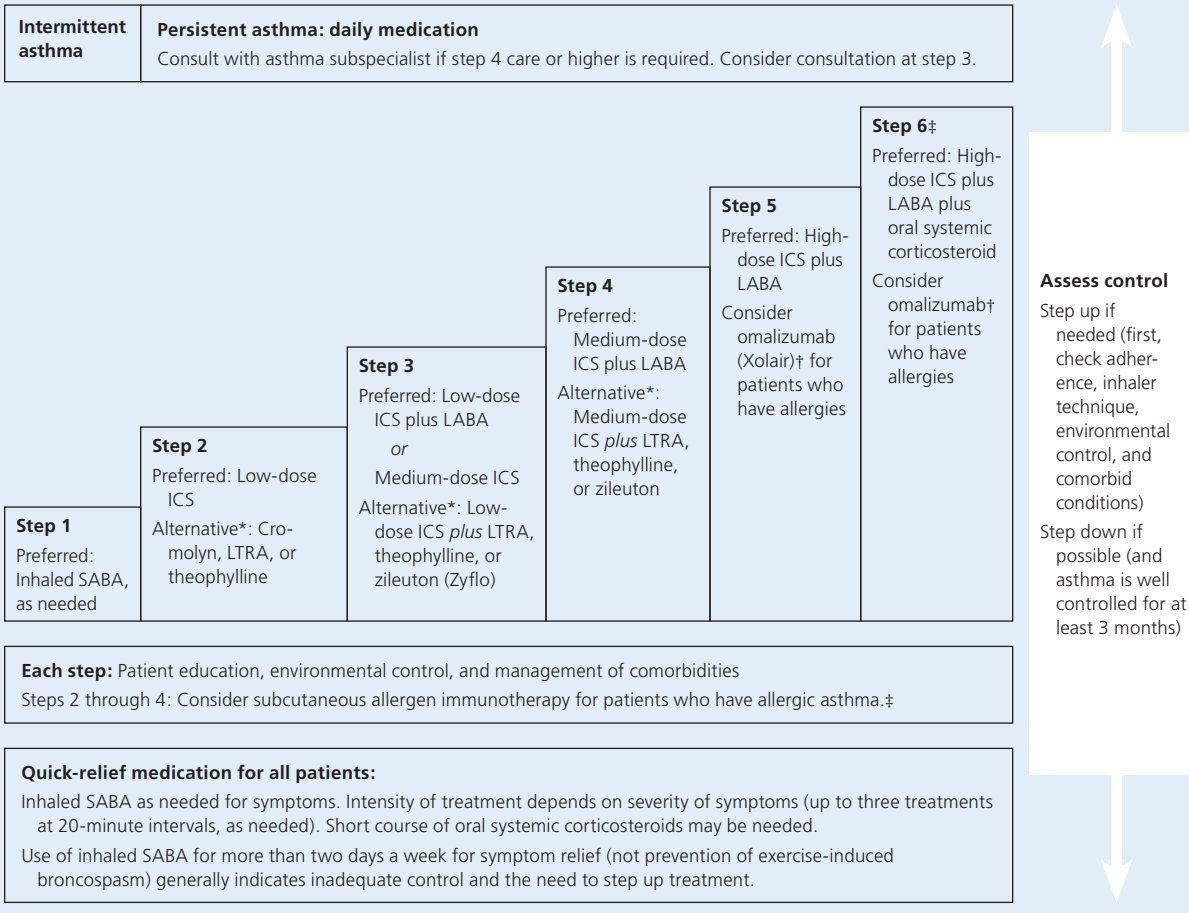
Figure 1. Classifying asthma severity in children 12 years and older and adults. (EIB = exercise-induced bronchospasm; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity.)

Adapted from National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program. Expert panel report 3: guidelines for the diagnosis and management of asthma. Bethesda, Md.: National Heart, Lung, and Blood Institute; Revised August 2007:74. NIH publication no. 07-4051. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed March 11, 2016.

symptom control at subsequent visits (every two to four weeks), increasing the intensity of therapy as needed if control is not initially achieved. Step-down therapy starts with patients receiving a high-dose regimen, the intensity of which is reduced as control is achieved. The latter approach could be preferred, for example, to obtain rapid control in a patient who has significant symptoms at the time of diagnosis. Steps 4 and 5 within the EPR-3 Stepwise Approaches, which recommend the use of a medium- or high-dose inhaled corticosteroid plus a long-acting $beta_2$ agonist (LABA), are common starting points in step-down therapy.

A small randomized trial found that patients with moderate persistent asthma who were started on a high-

Stepwise Approach for Managing Asthma in Children 12 Years and Older and Adults



NOTE: *The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs. Treatment options are listed in alphabetical order. Step 1, 2, and 3 preferred therapies are based on Evidence A (randomized controlled trials, rich body of data); step 3 alternative therapy is based on Evidence A for LTRA, Evidence B (randomized controlled trials, limited body of data) for theophylline, and Evidence D (panel consensus judgment) for zileuton. Step 4 preferred therapy is based on Evidence B, and alternative therapy is based on Evidence B for LTRA and theophylline and Evidence D for zileuton. Step 5 preferred therapy is based on Evidence B. Step 6 preferred therapy is based on National Heart, Lung, and Blood Institute Expert Panel Report 2 (1997) and Evidence B for omalizumab.*

**—If alternative treatment is used and response is inadequate, discontinue and use the preferred treatment before stepping up. Zileuton is a less desirable alternative because of limited studies on its use as adjunctive therapy and the need to monitor liver function. Theophylline requires monitoring of serum concentration levels.*

†—Clinicians who administer immunotherapy or omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur. Immunotherapy for steps 2 through 4 is based on Evidence B (randomized controlled trials, limited body of data) for house dust mites, animal dander, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergies in asthma is greater in children than in adults.

‡—Before oral systemic corticosteroids are introduced, a trial of a high-dose ICS plus LABA plus either LTRA, theophylline, or zileuton may be considered, although this approach has not been studied in clinical trials.

Figure 2. Stepwise approach for managing asthma in children 12 years and older and adults. (ICS = inhaled corticosteroid; LABA = long-acting beta$_2$ agonist; LTRA = leukotriene receptor antagonist; SABA = short-acting beta$_2$ agonist.)

Adapted from National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program. Expert panel report 3: guidelines for the diagnosis and management of asthma. Bethesda, Md.: National Heart, Lung, and Blood Institute; Revised August 2007:343. NIH publication no. 07-4051. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed March 11, 2016.

dose corticosteroid followed by the step-down approach experienced a more prompt improvement in respiratory function and asthma symptoms, as well as a lower maintenance dose of inhaled corticosteroids, compared with patients treated with a step-up approach.[11] The EPR-3 guidelines advise that treatment generally be maintained at a high-dose level with patients experiencing good symptom control for three months before stepping down in intensity; reliable patients with well-controlled asthma may be able to step down earlier. Physicians

should monitor symptom control in the period after a step down in therapy because patients may have increased symptoms, particularly when an LABA is discontinued.[12-14] Medications commonly used in these two approaches are listed in *Table 1*, with additional information on dosing and adverse effects for these drugs available in *eTable A*.

Table 1. Common Asthma Medications

Short-acting bronchodilators	**Long-acting beta$_2$ agonists**
Albuterol DPI	Budesonide/formoterol (Symbicort)
Albuterol HFA	Fluticasone/salmeterol DPI (Advair Diskus)
Albuterol nebulized	Fluticasone/salmeterol HFA (Advair HFA)
Ipratropium/albuterol inhaled (Combivent)	Fluticasone/vilanterol (Breo Ellipta)
Ipratropium/albuterol nebulized (Duoneb)	**Leukotriene receptor antagonists**
Levalbuterol HFA (Xopenex HFA)	Montelukast (Singulair)
Levalbuterol nebulized (Xopenex)	Zafirlukast (Accolate)
Inhaled corticosteroids	**Leukotriene inhibitor**
Beclomethasone HFA	Zileuton (Zyflo)
Budesonide DPI (Pulmicort)	**Methylxanthines**
Budesonide nebulized (Pulmicort)	Theophylline
Ciclesonide HFA (Alvesco)	**Cromolyn**
Flunisolide HFA (Aerospan)	**Monoclonals**
Fluticasone furoate DPI (Arnuity Ellipta)	Omalizumab (Xolair)
Fluticasone propionate DPI (Flovent Diskus)	
Fluticasone propionate HFA (Flovent HFA)	
Mometasone DPI (Asmanex)	
Mometasone HFA (Asmanex HFA)	

DPI = dry powder inhaler; HFA = hydrofluoroalkane.

Inhaled Corticosteroids

Inhaled corticosteroids are the most effective long-term medication for asthma.[10,15-18] They have been shown to reduce symptom severity, systemic steroid use, emergency department visits, hospitalizations, and deaths caused by asthma, and improve asthma control, quality of life, and objective measures of lung function.[10,15-18] Adverse effects of inhaled corticosteroids are limited, with only a slight effect on linear growth of approximately 0.5 cm per year noted in children. The effect on linear growth lessens after the first year of medication use and seems to be independent of patient age or the type of corticosteroid, dose, or delivery mechanism. It is unclear if inhaled corticosteroid use has an impact on final adult height.[19] Other adverse effects, such as dysphonia, are generally self-limited or may be improved by changing the delivery mechanism of the inhaled corticosteroid.[20]

There are clinically significant differences in patient response to corticosteroids that are associated with age, race, and risk factors such as smoking. Black children and smokers have an increased risk of corticosteroid insensitivity.[21,22] In general, delivery mechanism and type of steroid have little impact on the clinical effectiveness of corticosteroids, with the notable exception of a spacer device, which can result in a 20% to 30% increase in the amount of medication that is deposited in the lungs.[23] Dosing of inhaled corticosteroids should be managed in a step-up or step-down fashion based on an assessment of symptom control and severity *(Figure 2, eFigure C, and eFigure D)*.[10] Whereas abrupt cessation of inhaled corticosteroids predisposes patients to acute asthma exacerbations, changing the dosage of an inhaled corticosteroid does not increase exacerbation risk.[24,25]

Long-Acting Beta$_2$ Agonists

LABAs are effective for the control of persistent asthma symptoms. They initially have an action of more than 12 to 24 hours. Available non-combination LABAs include salmeterol (Serevent) and formoterol (Foradil). Duration of action decreases to less than five hours with chronic regular use of LABAs,[10] excluding those that contain vilanterol which currently lack data regarding duration of action decrease. The addition of an LABA to inhaled corticosteroid therapy is superior to the addition of leukotriene receptor antagonists (LTRAs) to inhaled corticosteroids in reducing asthma exacerbations requiring oral corticosteroid use, as well as improving quality-of-life measures and the effects and frequency of rescue inhaler use.[26] Current evidence shows no clear difference in the risk of fatal adverse events between LABA monotherapy and combination therapy with inhaled corticosteroids. The risk of nonfatal adverse events is increased with salmeterol monotherapy, but it is not significantly increased with either formoterol monotherapy or combination therapy with inhaled corticosteroids and either LABA option.[27] Current recommendations discourage the use of LABA monotherapy for long-term control of asthma.[10]

Combination Therapy

The combination of an inhaled corticosteroid and an LABA is considered a preferred therapy by the EPR-3 for the control of moderate persistent asthma in children five to 11 years of age and those 12 years and older.[10] Combination therapy offers the best prevention of severe asthma

BEST PRACTICES IN PULMONARY MEDICINE – RECOMMENDATIONS FROM THE CHOOSING WISELY CAMPAIGN

Recommendation	*Sponsoring organization*
Do not diagnose or manage asthma without spirometry.	American Academy of Allergy, Asthma and Immunology

Source: For more information on the Choosing Wisely Campaign, see http://www.choosingwisely.org. For supporting citations and to search Choosing Wisely recommendations relevant to primary care, see http://www.aafp.org/afp/recommendations/search.htm.

exacerbations.[28] A 2013 study confirmed the overall safety of combination inhaled corticosteroid and LABA therapy, especially compared with LABA monotherapy.[29] Combination therapy dosing should be managed in a step-up or step-down approach similar to the management of inhaled corticosteroid therapy. Slight differences in when to start combination therapy are noted between the EPR-3 and Global Initiative for Asthma (GINA) guidelines.[10,30] For example, according to step 3 of the EPR-3 stepwise approach for patients 12 years and older, either a low-dose inhaled corticosteroid plus an LABA, or a medium-dose inhaled corticosteroid alone is appropriate *(Figure 2)*.[10] The GINA guidelines recommend a low-dose inhaled corticosteroid plus an LABA as the preferred selection in this age group, with a medium-dose inhaled corticosteroid considered the secondary option.

Leukotriene Modifiers

Leukotriene modifiers include LTRAs and leukotriene inhibitors, which both act as anti-inflammatory medications. LTRAs block leukotriene receptors, whereas leukotriene inhibitors block the production of 5-lipoxygenase. The two LTRAs licensed in the United States are montelukast (Singulair) and zafirlukast (Accolate). LTRAs may be used as monotherapy for mild persistent asthma, but are considered second-line agents based on the EPR-3[10] and GINA guidelines.[30] For mild to moderate asthma, the risk of exacerbation is approximately 50% less in patients prescribed an inhaled corticosteroid compared with those prescribed an LTRA.[15] A 2014 Cochrane review found an LABA plus inhaled corticosteroid to be modestly superior to an LTRA plus inhaled corticosteroid in adults with inadequately controlled asthma.[26] LTRAs are best used to improve pulmonary function in patients with aspirin-sensitive asthma[31] and to decrease symptoms in exercise-induced bronchospasm.[32,33] They should also be considered in patients with mild persistent asthma who prefer not to use inhaled corticosteroids. Although LTRAs generally have few adverse effects, physicians should be aware of rare case reports of eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), psychiatric symptoms, hypertriglyceridemia, angioedema, urticaria, and glomerulonephritis.[34]

Leukotriene inhibitors, such as zileuton (Zyflo), are a more recent addition to the treatment of asthma. Limited data show some improvement in peak flows with zileuton compared with montelukast.[35] However, zileuton is extremely expensive and has not been shown to improve symptom scores.

Methylxanthines

Theophylline, the most commonly used methylxanthine in asthma patients, acts as a bronchodilator at high serum concentrations (10 to 20 mcg per L [56 to 111 µmol per L]), but has an anti-inflammatory effect at lower serum concentrations (5 to 10 mcg per L [28 to 56 µmol per L]).[36,37] Theophylline administered with inhaled corticosteroids decreases exacerbations,[38] but it has similar effects to increasing the dosage of the inhaled corticosteroid.[39,40] The EPR-3 specifies that theophylline is a nonpreferred alternative to inhaled corticosteroid.[10] The GINA guidelines recommend a trial of increased dosage of inhaled corticosteroid before considering theophylline, unless steroid sparing is necessary, such as in patients with severe glaucoma or active tuberculosis infection.[30] Patients in developing countries are more likely to use low-dose theophylline than inhaled corticosteroids because it is a cheaper option.[39,40] Although theophylline is considered safer at lower serum concentrations, care of patients who use theophylline should be comanaged with an asthma subspecialist because of the narrow therapeutic range of this drug and the risk of death from an overdose.[36,40] Theophylline is metabolized in the liver and is susceptible to drug-drug interactions through cytochrome P450 1A2 *(Table 2)*.[37,41]

Table 2. Common Drug-Drug Interactions with Theophylline

Medication or substance	*Approximate effect on serum levels of theophylline*
Alcohol	30% increase
Ciprofloxacin	40% increase
Diltiazem	Increase or no effect
Erythromycin	35% increase
Oral contraceptives	30% increase
Phenytoin (Dilantin)	40% decrease
Propranolol	100% increase
Verapamil	20% increase

Information from references 37 and 41.

Table 3. Select Complementary and Alternative Asthma Treatments

Name	*Comments*	*Effectiveness for treatment*
Black seed (*Nigella sativa*)	One small RCT showed improved pulmonary function testing and decreased symptoms compared with placebo.[59] Effect on pulmonary function testing was less than with theophylline.[60]	Possibly effective
Butterbur	Traditionally used in Taiwan to treat asthma. Has anti-inflammatory properties.[61] A small non-randomized open trial showed 48% decrease in exacerbations, and 40% of patients were able to reduce their dosage of inhaled corticosteroids, but results potentially biased due to study design. Blinded RCT is needed to determine true benefit and adverse effects.[62]	Possibly effective
Caffeine	Improves airway function for up to four hours and may impact pulmonary function testing. No evidence that results have clinical or quality-of-life significance.[63]	Not effective
Fish oil (omega-3)	Theoretically acts to decrease inflammation. Studies of its effectiveness have inconsistent results and are poorly designed. A large, well-designed RCT is needed to determine if there is any benefit.[64]	Effectiveness unknown
Ginkgo	No clinical evidence available. Effect on asthma is theoretical via anti-inflammatory effect in an animal model.[65] Increases metabolism of theophylline by four times via cytochrome P450 1A2.[66]	Effectiveness unknown
Homeopathy	A 2004 Cochrane review found no evidence of benefit, citing a lack of quality studies.[67]	Not effective
Magnesium	Associated with bronchodilatory and anti-inflammatory effects. Small, blinded RCT showed improved peak expiratory flow and quality of life and decreased bronchial activity with 340 mg of supplementation per day. Larger RCT is needed.[68]	Possibly effective
Pycnogenol	Small, blinded RCT showed improved peak expiratory flow and decreased use of rescue medication compared with placebo group.[69] A 2012 Cochrane review concluded insufficient evidence is available.[70] Larger RCT is needed.	Possibly effective
Soy	Small RCT showed no significant difference compared with placebo.[71]	Not effective
Vitamins C and E	Associated with anti-inflammatory effects. A 2014 Cochrane review found insufficient evidence due to limited small studies and lack of clinically important end points.[72]	Effectiveness unknown
Vitamin D	Used to treat deficiency associated with severe asthma[73]; however, an RCT showed vitamin D_3 supplementation had no effect on exacerbation rate in vitamin D–deficient patients with asthma.[74]	Not effective

RCT = randomized controlled trial.

Information from references 59 through 74.

Cromolyn

Cromolyn decreases bronchospasm through an anti-inflammatory effect.[42] A 2008 Cochrane review found insufficient evidence of benefit of cromolyn over placebo.[43] Because cromolyn is less effective and less cost-effective than an inhaled corticosteroid, its use should be limited to patients who cannot tolerate inhaled corticosteroids.[44] Cromolyn is beneficial for exercise-induced bronchospasm but is considered second-line therapy.[44,45]

Monoclonal Antibodies

Omalizumab (Xolair) is currently the only monoclonal anti-immunoglobulin E (IgE) antibody with a U.S. Food and Drug Administration indication for asthma.[46] It binds the free IgE antibodies, decreasing the release of inflammatory mediators from mast cells. In a randomized trial, omalizumab reduced the rate of exacerbations in inner-city children from 48.8% to 30.3%, resulting in decreased reliance on an inhaled corticosteroid.[47] A 2014 Cochrane review found omalizumab effective in reducing exacerbations, decreasing the dosage of inhaled corticosteroid used, and improving health-related quality of life.[48] Because of its high cost and the risk of anaphylaxis, omalizumab should be considered only for adults and children 12 years and older with confirmed IgE-dependent allergic asthma that is uncontrolled with conventional medications.[49,50]

Immunotherapy

Subcutaneous and sublingual immunotherapies involve repeated patient exposure to antigens to desensitize the patient to the antigen. Immunotherapy is effective in reducing exacerbations, need for medication use, and overall cost of care in patients with allergic asthma.[51-53]

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
Inhaled corticosteroids improve asthma control and quality of life and reduce asthma symptom severity, systemic steroid use, emergency department visits and hospitalizations, and deaths.	A	10, 15-18
Long-acting beta$_2$ agonists are effective for control of persistent asthma symptoms and are the preferred agents to add to inhaled corticosteroids in patients 12 years and older, but they are not recommended for use as monotherapy.	A	10, 27, 29
Leukotriene receptor antagonists can be used as adjunctive therapy with inhaled corticosteroids, but they are less effective than long-acting beta$_2$ agonists in patients 12 years and older.	B	10, 15, 26
If adequate symptom control is not attained with low-dose inhaled corticosteroids, either increasing the inhaled steroid dosage or adding a long-acting beta$_2$ agonist to therapy is appropriate according to current guideline recommendations.	B	10, 30

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.

A 2010 Cochrane review found a number needed to treat of 4 to avoid one deterioration in asthma symptoms, but it could not determine the size of effect compared with other therapies.[54] Immunotherapy should be considered in patients with asthma triggered by confirmed allergies who are experiencing adverse effects from medication or have other comorbid allergic conditions.

Alternative Treatments

The rate of complementary and alternative medicine (CAM) use in children and adolescents with asthma is as high as 71% to 84%, but 54% of parents do not disclose the use of these methods.[55,56] CAM use is more common among children with poorly controlled asthma and those with barriers to treatment.[57,58] However, data indicate that CAM treatment is typically not used as a substitute for conventional medicine.[57] Patients who are receiving CAM substances should be cautioned that there is little regulation to ensure the consistency and purity of the contents and that CAM is never a substitute for rescue medication. Common CAM treatments and their effects on asthma symptoms are listed in *Table 3*.[59-74]

Data Sources: A PubMed search was completed in Clinical Queries using the key terms asthma, inhaled corticosteroids, leukotriene receptor antagonist, long-acting beta$_2$ agonists, and omalizumab. The search included meta-analyses, randomized controlled trials, clinical trials, and reviews. Also searched were Cochrane Database of Systematic Reviews, Essential Evidence Plus, and Natural Medicines Comprehensive Database. Search dates: January 15, 2015 and August 20, 2015.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the U.S. Air Force Medical Department or the U.S. Air Force at large.

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Classifying Asthma Severity in Children 0 to 4 Years of Age

Classifying severity in patients who are not currently receiving long-term control medication*

Components of severity		*Classification of asthma severity*			
		Intermittent	*Persistent*		
			Mild	*Moderate*	*Severe*
Impairment	Symptoms	≤ 2 days per week	> 2 days per week but not daily	Daily	Throughout the day
	Nighttime awakenings	0	1 to 2 times per month	3 to 4 times per month	> 1 time per week
	Short-acting $beta_2$ agonist use for symptom control (not prevention of EIB)	≤ 2 days per week	> 2 days per week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Risk	Exacerbations requiring oral systemic corticosteroids	0 to 1 per year†	≥ 2 exacerbations in 6 months requiring oral corticosteroids, or ≥ 4 wheezing episodes in 1 year lasting > 1 day and risk factors for persistent asthma†		
		Consider severity and interval since last exacerbation; frequency and severity may fluctuate over time			
		Exacerbations of any severity may occur in patients in any severity category			

Classifying severity in patients after asthma becomes well controlled, by lowest level of treatment required to maintain control‡

	Classification of asthma severity			
	Intermittent	*Persistent*		
		Mild	*Moderate*	*Severe*
Lowest level of treatment required to maintain control (see eFigure C for treatment steps)	Step 1	Step 2	Step 3 or 4	Step 5 or 6

**—Level of severity is determined by assessment of impairment and risk. Assess impairment domain by caregiver's recall of previous two to four weeks. Assign severity to the most severe category in which any feature occurs.*

†—At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. For treatment purposes, patients who had at least two exacerbations requiring oral systemic corticosteroids in the past six months, or at least four wheezing episodes in the past year, and who have risk factors for persistent asthma may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

‡—For population-based evaluations, clinical research, or characterization of a patient's overall asthma severity after control is achieved. For clinical management, the focus is on monitoring the level of control, not the level of severity, once treatment is established.

eFigure A. Classifying asthma severity in children 0 to 4 years of age. (EIB = exercise-induced bronchospasm.)

Adapted from National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program. Expert panel report 3: guidelines for the diagnosis and management of asthma. Bethesda, Md.: National Heart, Lung, and Blood Institute; Revised August 2007:72. NIH publication no. 07-4051. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed March 11, 2016.

Classifying Asthma Severity in Children 5 to 11 Years of Age

Classifying severity for patients who are not currently receiving long-term control medication*

Components of severity		*Classification of asthma severity*			
		Intermittent	*Persistent*		
			Mild	*Moderate*	*Severe*
Impairment	Symptoms	≤ 2 days per week	> 2 days per week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤ 2 times per month	3 to 4 times per month	> 1 time per week but not nightly	Every night
	Short-acting beta$_2$ agonist use for symptom control (not prevention of EIB)	≤ 2 days per week	> 2 days per week but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	Normal FEV_1 between exacerbations FEV_1 > 80% predicted FEV_1/FVC > 85%	FEV_1 ≥ 80% predicted FEV_1/FVC > 80%	FEV_1 60% to 80% predicted FEV_1/FVC 75% to 80%	FEV_1 < 60% predicted FEV_1/FVC < 75%
Risk	Exacerbations requiring oral systemic corticosteroids	0 to 1 per year†	≥ 2 in one year†	≥ 2 in one year†	≥ 2 in one year†
		Consider severity and interval since last exacerbation; frequency and severity may fluctuate over time for patients in any severity category			
		Relative annual risk of exacerbations may be related to FEV_1			

Classifying severity in patients after asthma becomes well controlled, by lowest level of treatment required to maintain control‡

	Classification of asthma severity			
	Intermittent	*Persistent*		
		Mild	*Moderate*	*Severe*
Lowest level of treatment required to maintain control (see eFigure D for treatment steps)	Step 1	Step 2	Step 3 or 4	Step 5 or 6

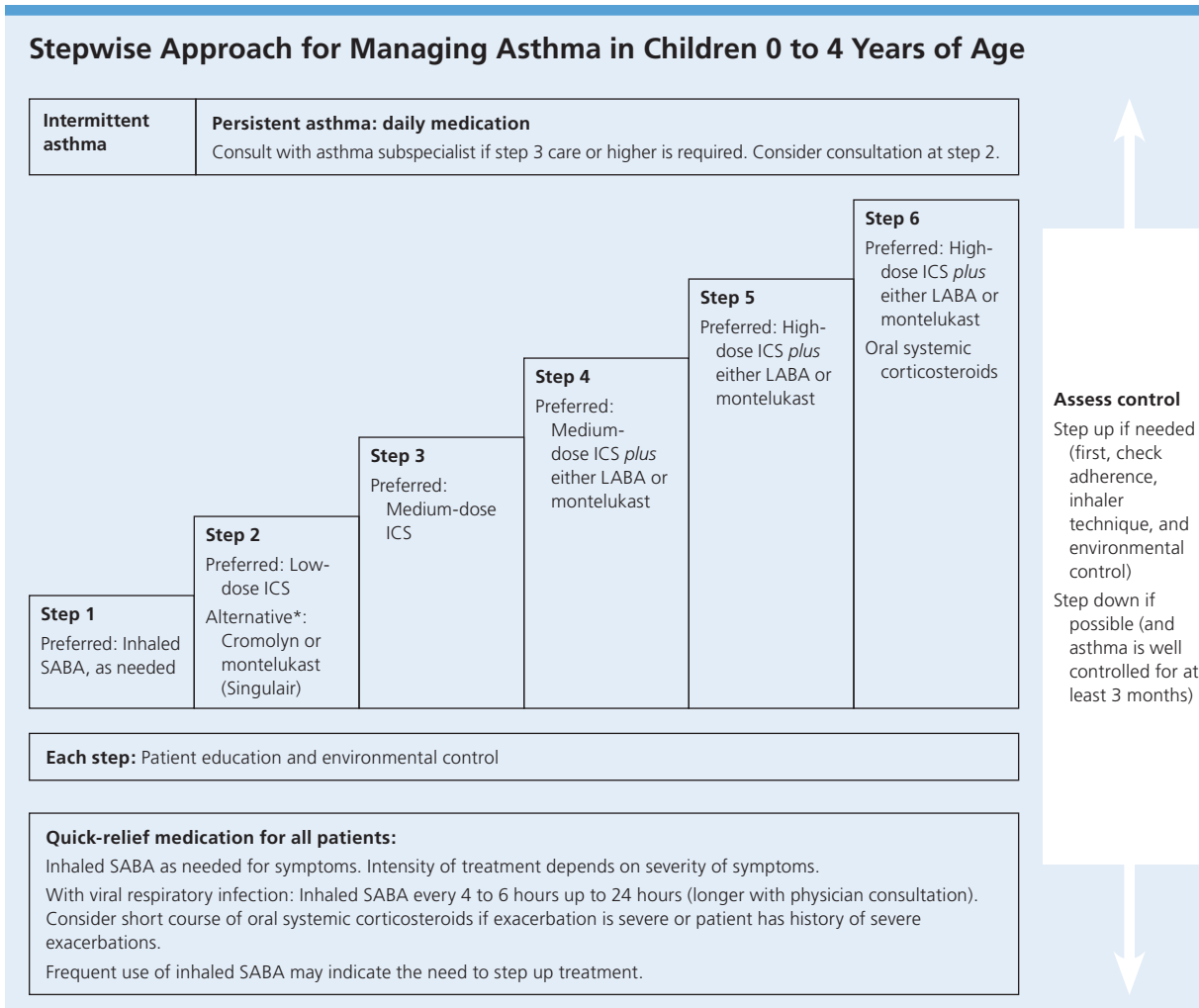
**—Level of severity is determined by assessment of impairment and risk. Assess impairment domain by patient's or caregiver's recall of previous two to four weeks and spirometry. Assign severity to the most severe category in which any feature occurs.*

†—At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or admission to intensive care unit) indicate greater underlying disease severity. For treatment purposes, patients who had at least two exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

‡—For population-based evaluations, clinical research, or characterization of a patient's overall asthma severity after control is achieved. For clinical management, the focus is on monitoring the level of control, not the level of severity, once treatment is established.

eFigure B. Classifying asthma severity in children 5 to 11 years of age. (EIB = exercise-induced bronchospasm; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity.)

Adapted from National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program. Expert panel report 3: guidelines for the diagnosis and management of asthma. Bethesda, Md.: National Heart, Lung, and Blood Institute; Revised August 2007:73. NIH publication no. 07-4051. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed March 11, 2016.



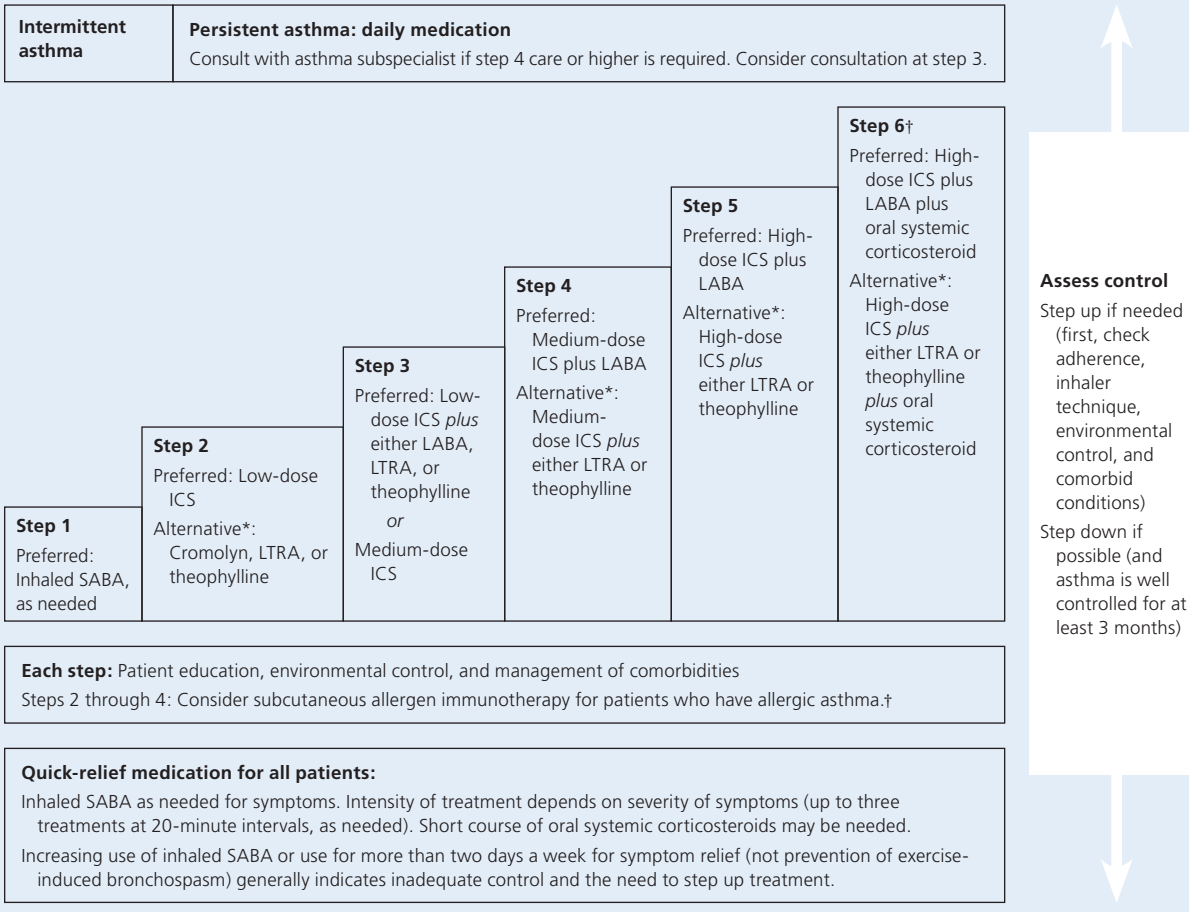
NOTE: *The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs. Treatment options are listed in alphabetical order. If clear benefit is not observed within four to six weeks and patient or family medication technique and adherence are satisfactory, consider adjusting therapy or alternative diagnosis. Studies on children 0 to 4 years of age are limited. Step 2 preferred therapy is based on Evidence A (randomized controlled trials, rich body of data). All other recommendations are based on expert opinion and extrapolation from studies in older children.*

**—If alternative treatment is used and response is inadequate, discontinue and use the preferred treatment before stepping up.*

eFigure C. Stepwise approach for managing asthma in children 0 to 4 years of age. (ICS = inhaled corticosteroid; LABA = long-acting beta$_2$ agonist; SABA = short-acting beta$_2$ agonist.)

Adapted from National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program. Expert panel report 3: guidelines for the diagnosis and management of asthma. Bethesda, Md.: National Heart, Lung, and Blood Institute; Revised August 2007:305. NIH publication no. 07-4051. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed March 11, 2016.

Stepwise Approach for Managing Asthma in Children 5 to 11 Years of Age



NOTE: *The stepwise approach is meant to assist, not replace, the clinical decision making required to meet individual patient needs. Treatment options are listed in alphabetical order. Step 1 and step 2 medications are based on Evidence A (randomized controlled trials, rich body of data). Step 3 ICS plus adjunctive therapy and ICS are based on Evidence B (randomized controlled trials, limited body of data) for effectiveness of each treatment and extrapolation from comparator trials in older children 12 to 17 years of age and adults. Comparator trials are not available for the 5- to 11-year-old age group; steps 4 through 6 are based on expert opinion and extrapolation from other studies in older children and adults.*

**—If alternative treatment is used and response is inadequate, discontinue and use the preferred treatment before stepping up. Theophylline is a less desirable alternative because of the need to monitor serum concentration levels.*

†—Immunotherapy for steps 2 through 4 is based on Evidence B (randomized controlled trials, limited body of data) for house dust mites, animal dander, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergies in asthma is greater in children than adults. Clinicians who administer immunotherapy should be prepared and equipped to identify and treat anaphylaxis that may occur.

eFigure D. Stepwise approach for managing asthma in children 5 to 11 years of age. (ICS = inhaled corticosteroid; LABA = long-acting beta$_2$ agonist; LTRA = leukotriene receptor antagonist; SABA = short-acting beta$_2$-agonist.)

Adapted from National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program. Expert panel report 3: guidelines for the diagnosis and management of asthma. Bethesda, Md.: National Heart, Lung, and Blood Institute; Revised August 2007:306. NIH publication no. 07-4051. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed March 11, 2016.

eTable A. Common Asthma Medications

Drug	*Dosage*	*Adverse effects*
Short-acting bronchodilators		
Albuterol DPI	Age > 11 years: 180 mcg every 4 to 6 hours as needed	Same as albuterol nebulized
Albuterol HFA	Age 4 to 11 years: 180 mcg every 4 to 6 hours as needed Age > 11 years: 180 mcg every 4 to 6 hours as needed	Same as albuterol nebulized
Albuterol nebulized	Age < 2 years: 0.05 to 0.15 mg per kg every 1 to 6 hours as needed, max 1.25 mg per dose Age 2 to 5 years: 0.1 to 0.15 mg per kg every 4 to 6 hours as needed, max 2.5 mg per dose Age 5 to 11 years: 2.5 mg every 4 to 6 hours as needed, max 10 mg per day Age > 11 years: 2.5 to 10 mg every 1 to 4 hours as needed	Angina, arrhythmia, bad taste, cough, dizziness, headache, hyperglycemia, hypertension, hypokalemia, nausea, nervousness, palpitations, tachycardia, throat irritation, tremor
Ipratropium/albuterol inhaled (Combivent)	Age < 13 years: 80 mcg/400 mcg to 160 mcg/800 mcg every 20 minutes as needed for up to 3 hours Age ≥ 13 years: 160 mcg/800 mcg every 20 minutes as needed for up to 3 hours	Same as ipratropium/albuterol nebulized
Ipratropium/albuterol nebulized (Duoneb)	Age < 13 years: 0.25 mg/1.25 mg to 0.5mg/2.5mg every 20 minutes for three doses, then as needed for up to 3 hours Age ≥ 13 years: 0.5 mg/2.5 mg every 20 minutes for 3 doses, then as needed for up to 3 hours	Angina, arrhythmia, cardiac arrest, glaucoma, hyperglycemia, hyperlactatemia, hypertension, hypokalemia, hypotension, pharyngitis
Levalbuterol HFA (Xopenex HFA)	Age 4 to 11 years: 90 mcg every 4 to 6 hours as needed, max 540 mcg per day Age > 11 years: 90 mcg every 4 to 6 hours as needed, max 540 mcg per day	Same as albuterol nebulized
Levalbuterol nebulized (Xopenex)	Age 6 to 11 years: 0.31 to 0.63 mg three times a day as needed, max dose 0.63 mg Age > 11 years: 0.63 to 1.25 mg three times a day as needed	Same as albuterol nebulized
Inhaled corticosteroids		
Beclomethasone HFA	Age 5 to 11 years: 40 to 160 mcg per day Age > 11 years: 40 to 640 mcg per day	Adrenal suppression, cataracts, cough, dysmenorrhea, dysphonia, eosinophilia, glaucoma, hypercorticism, growth suppression, Churg-Strauss syndrome, oral candidiasis, osteoporosis
Budesonide DPI (Pulmicort)	Age 6 to 11 years: 180 to 720 mcg per day Age > 11 years: 180 to 1,440 mcg per day	Same as beclomethasone HFA
Budesonide nebulized (Pulmicort)	Age 1 to 8 years: 0.25 to 1.0 mg daily	Same as beclomethasone HFA
Ciclesonide HFA (Alvesco)	Age > 11 years: 80 to 640 mcg per day	Same as beclomethasone HFA
Flunisolide HFA (Aerospan)	Age 6 to 11 years: 160 to 320 mcg per day Age > 11 years: 160 to 640 mcg per day	Same as beclomethasone HFA
Fluticasone furoate DPI (Arnuity Ellipta)	Age > 11 years: 100 to 200 mcg per day	Same as beclomethasone HFA
Fluticasone propionate DPI (Flovent Diskus)	Age 4 to 11 years: 100 to 200 mcg per day Age > 11 years: 100 to 1,000 mcg per day	Same as beclomethasone HFA
Fluticasone propionate HFA (Flovent HFA)	Age 4 to 11 years: 88 to 176 mcg per day Age > 11 years: 88 to 880 mcg per day	Same as beclomethasone HFA

continues

eTable A. Common Asthma Medications *(continued)*

Drug	*Dosage*	*Adverse effects*
Inhaled corticosteroids *(continued)*		
Mometasone DPI (Asmanex)	Age 4 to 11 years: 110 mcg per day Age > 11 years: 220 to 440 mcg per day	Same as beclomethasone HFA
Mometasone HFA (Asmanex HFA)	Age > 11 years: 400 to 800 mcg per day	Same as beclomethasone HFA
Long-acting beta$_2$ agonists		
Budesonide/formoterol (Symbicort)	Age > 11 years: 320 mcg/18 mcg to 640 mcg/18 mcg per day	Adrenal suppression, angina, arrhythmia, cardiac arrest, cataracts, cough, dysmenorrhea, dysphonia, eosinophilia, glaucoma, growth suppression, hypercorticism, hyperglycemia, hypertension, hypokalemia, hypotension, oral candidiasis, osteoporosis, palpitations, Churg-Strauss syndrome, tremor
Fluticasone/salmeterol DPI (Advair Diskus)	Age 4 to 11 years: 200 mcg/100 mcg per day Age > 11 years: 200 mcg/100 mcg to 1,000 mcg/100 mcg per day	Same as budesonide/formoterol
Fluticasone/salmeterol HFA (Advair HFA)	Age > 11 years: 180 mcg/84 mcg to 920 mcg/84 mcg per day	Same as budesonide/formoterol
Fluticasone/vilanterol (Breo Ellipta)	Age ≥ 18 years: 100 mcg/25 mcg to 200 mcg/25 mcg per day	Same as budesonide/formoterol
Leukotriene receptor antagonists		
Montelukast (Singulair)	Age 1 to 5 years: 4 mg every evening Age 6 to 14 years: 5 mg every evening Age ≥ 15 years: 10 mg every evening	Cough, dyspepsia, fatigue, gastroenteritis, headache, nasal congestion, Churg-Strauss syndrome, rare elevations of LFTs, rash[A1]
Zafirlukast (Accolate)	Age 5 to 11 years: 10 mg twice a day Age ≥ 12 years: 20 mg twice a day	Diarrhea, headache, nausea, Churg-Strauss syndrome, rare elevations of LFTs[A2]
Leukotriene inhibitor		
Zileuton (Zyflo)	Age > 12 years: 600 mg four times a day	Abdominal pain, dyspepsia, headache, myalgia, nausea; rare sleep disorders and behavior changes[A3]
Methylxanthines		
Theophylline	300 to 600 mg by mouth, divided, twice a day	Serum level < 20 mg per L (111 µmol per L): Headache, insomnia, nausea, vomiting Serum level > 20 mg per L: Arrhythmias, seizures[A4]
Cromolyn	20-mg inhalation nebulizer four times a day	Cough, nasal congestion, nausea, sneezing, wheezing[A5]
Monoclonals		
Omalizumab (Xolair)	Age > 12 years: 150 to 375 mg subcutaneously every 2 to 4 weeks	Headache, injection site reaction, pharyngitis, sinusitis, upper respiratory tract infection, viral infections[A6]

DPI = dry powder inhaler; HFA = hydrofluoroalkane; LFT = liver function tests.

Information from:

A1. Singulair (montelukast) [package insert]. Whitehouse Station, N.J.: Merck; 2016. https://www.merck.com/product/usa/pi_circulars/s/singulair/singulair_pi.pdf. Accessed July 28, 2016.

A2. Accolate (zafirlukast) [package insert]. http://druginserts.com/lib/rx/meds/accolate-2/. Accessed August 20, 2015.

A3. Zyflo (zileuton) [package insert]. http://druginserts.com/lib/rx/meds/zyflo-1/. Accessed August 20, 2015.

A4. Theophylline [package insert]. http://druginserts.com/lib/rx/meds/theophylline-8/. Accessed August 20, 2015.

A5. Cromolyn sodium [package insert]. http://druginserts.com/lib/rx/meds/cromolyn-sodium-8/. Accessed August 20, 2015.

A6. Xolair (omalizumab) [package insert]. East Hanover, N.J.: Novartis; 2016. http://www.gene.com/download/pdf/xolair_prescribing.pdf. Accessed July 25, 2016.